The Relationship between Age of Thrombus and Outcomes of Cerebral Venous Sinus Thrombosis in Neurological Institute of Thailand

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Abstract

Background: The primary thrombus component is fibrin fiber (~60%), with platelets, erythrocytes, and leukocytes constituting the remainder (~40%). Thrombus strength and viscoelasticity are highly associated with fibrin features at the molecular level. With high fibrin density, the clot had been observed to be more rigid, less permeable, and more resistant to fibrinolysis.

Objective: Therefore, we were interested in acute and early subacute stages of thrombus as the main measures because, in those stages, thrombus formation may resist anticoagulant due to high fibrin density. As a result, this study may provide a reference for clinicians to optimize their clinical decision to make early appropriate management in patient with acute or early subacute stage of thrombus.

Methods: Retrospective single-center analysis of 39 patients with CVST who were hospitalized in Neurological Institute of Thailand, during 5 years between October 2015 and October 2020. The diagnosis and estimated age of thrombus was confirmed using conventional MRI. The correlation between subacute stage of intramural thrombus and functional outcome at discharge and follow up of the CVST patients were summarized and analyzed by Fisher's exact test.

Results: Data were derived from the Neurological Institute of Thailand. Among our 39 patients, 74.4% were women, and 25.6% were men. The median age of the overall population was 40, with a range of 18-78 years. Headache is the most frequent symptom, present in 74.4% of the patients. The most frequency of risk factors of CVST were OCP consumption in women (38.5%). Most of the patients

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in both groups had neurological improvement. No significant correlation was found between the age of the thrombus and disease progression (P = 0.336) or complications (P = 1.000). Although there was a significant correlation between functional outcome at discharge and age of thrombus (P = *0.046*), by acute stage of thrombus had a good outcome of 53.8% and a poor outcome of 46.2%, while all of the early subacute stages of thrombus had a good outcome.

Conclusion: Our study reveals that age of thrombus from T1-weight and T2-weight sequence MR imaging (MRI) were correlation with functioning outcome at discharge. overall outcome in our study was good in both acute and early subacute stage of thrombus.

Keywords: Venous thrombosis, Fibrin formation, Age of thrombus

Introduction

Thrombosis of the dural sinus and/or cerebral veins (CVST) is an uncommon form of stroke, usually affecting young individuals.[1] Despite advances in the recognition of CVST in recent years, diagnosis and management can be difficult because of the diversity of underlying risk factors. Anticoagulation remains the principal therapy and aims at preventing thrombus propagation and increasing recanalization.[2] Many invasive therapeutic procedures have been reported to treat CVST. These include chemical thrombolysis and direct mechanical thrombectomy with or without thrombolysis but there are no randomized controlled trials to support these interventions compared with anticoagulation.[2]

Although patients with CVST may recover with anticoagulation therapy, 9% to 13% have poor outcomes despite anticoagulation. As the result of physical properties of a venous thrombus. The primary thrombus component is fibrin fibers (~60%) with platelets, erythrocytes and leukocytes constituting the remainder (~40%).[3] Thrombus strength and viscoelasticity are highly associated with fibrin features at the molecular level, including diameter, branching, cross-linking and meshwork pore size. With high fibrin density, the clot had been observed to be more rigid, less permeable, and more resistant to fibrinolysis. A general timeline for thrombus formation includes the following: (a) 1-2 days after initial injury, clot rich in fibrin and platelets with pockets of erythrocytes; (b) 7-14 days after clot presentation, cell infiltration begins, clot increase in density and stiffness, eventual replacement by other extracellular proteins including collagen; and (c) 28 days after clot presentation, remodeled vein wall, rich in cells.[3]

Therefore, in our study, we were interested in acute and early subacute stage of thrombus as the main measure because in those stages, intraluminal thrombus formation may resistance to anticoagulant due to high fibrin density. Anticoagulation alone may not dissolve a large and extensive thrombus, and the clinical condition may worsen even during heparin treatment.[2,4,5] Thereby, this study may provide a reference for clinicians to optimize their clinical decision to make early appropriate management in patient with acute or early subacute stage of thrombus.

Furthermore, a recent study found that factors such as extreme age, coma at onset, and hemorrhagic infarction were associated with a poor prognosis,[6-8] and one interesting study looked at the sum of the thrombosis degrees in the multiple vessels, measured as the clot burden score, including both cerebral veins and cerebral sinuses which revealed that clot

burden was associated with the prognosis of patients.[9] So, in our secondary outcome, we would record the relevant factor to compare the baseline at the onset of patients in both groups.

Materials and Methods

Patient enrollment

This study was conducted at the Neurological Institute of Thailand, a tertiary referral hospital in Bangkok, Thailand, which serves many patients from all over the country. From October 2015 to October 2020, retrospective data was gathered for all patients with a diagnosis of CVST (ICD-10-CM Diagnosis Code: I167) from documents recorded in the hospital registry system.

The inclusion criteria were as follows:

1. Age more than 15 years old
2. Patients who fulfilled the diagnostic criteria of CVST
3. Patients who received anticoagulation (IV heparin or SC LMWH)
4. The diagnosis was confirmed based on both T1-weight and T2-weight sequence magnetic resonance imaging (MRI)

The patients who had incomplete medical record or only performed one kind of imaging sequence on MRI were excluded.

All the patients with suspected CVST underwent a preliminary CT brain for initial evaluation. After that conventional MR imaging was performed. Consulting with radiologist was done for confirmation of diagnosis and estimation age of thrombus from predominant signal intensity on MR imaging.

Patient were divided into four groups based on signal intensity on T1 and T2 weight sequence as shown in Table 1.[10-12]

Table 1 Appearance of thrombus on T1WI and T2WI

Stage and No. of days	Cause	Appearances on T1WI	Appearance on T2WI
Acute (0-7 days)	DeoxyHb	Isointense	Hypointense
Early subacute (7-14 days)	Intracellular MethHb	Hyperintense	Hypointense
Late subacute (7-14 days)	Extracellular MethHb	Hyperintense	Hyperintense
Chronic (>15 days)	Hemosiderin	Isointense	Hyperintense

Data Collection

The data included demographic data, clinical signs and symptoms, the time from onset of symptoms occurred to diagnosis confirmed by MRI, CVST predisposing factor, Glasgow Coma Scale at admission, neuroimaging presentations, location of occluded sinus, estimated age of thrombus from predominant signal intensity according to MR imaging technique, duration of hospitalization, progression of disease, complication and Oxford handicap score (modified Rankin scale) at both discharge and the time of follow-up were recorded.

Treatment and Outcomes

If no major contraindication, all patients were administered enoxaparin at 1.0 mg/kg subcutaneously twice a day while in hospital followed by oral anticoagulants. The dose of anticoagulant was adjusted to maintain INR level 2.0-3.0, while the selection of

anticoagulant would be left to the physicians based on the individualized condition of each patient. After discharge, all patients continued warfarin for a minimum of 3-12 months or lifelong according to the underlying etiology[2] and functional outcome were reviewed from outpatient recorded document.

The modified Rankin scale (mRS) was evaluated at both discharge and outpatient follow-up to measure the functional outcomes. The mRS = 0-2 was defined as relatively favorable outcomes (independency), whereas mRS = 3-6 was poor (dependency or death). The primary endpoint was functional outcomes at discharge and 3 to 6 months outpatient follow-up.

Statistical Analysis

The study protocol was approved by the research ethics committee of Neurological Institute of Thailand. Descriptive statistics were performed to describe all CVST patients. Amount of each stage of thrombus were shown in chart. For continuous data were presented as median with minimum to maximum range. For categorical data, numbers and percentages for each category were tabulated. A Fisher's Exact Test analysis was established to identify relationship between age of thrombus and functional outcomes in acute and early subacute groups. Otherwise, Mann-Whitney test were used. All significant levels reported were 2-sided, and $P<0.05$ is considered to indicate a statistical significance. All analyses were performed using SPSS software version 17.0 for window

Results

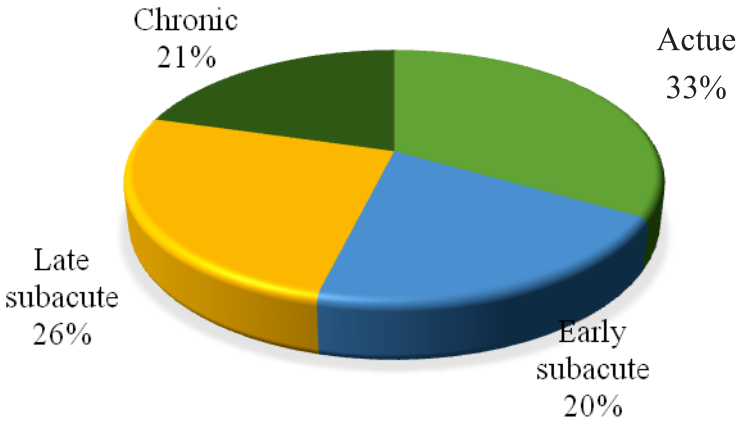
Between October 2015 to October 2020, 39 CVST patients were hospitalized in Neurological Institute of Thailand. No patients were lost to follow up. Among our 39 patients, 29 (74.4%) were women and 10 (25.6%) were men. The median age of the overall population was 40 with a range from 18-78 years. The overall of neurological symptoms and signs were summarized in the Table 2. Headache is the most frequent symptom, present in 74.4% of the patients. Other often occurring symptoms were motor weakness (41%), seizure (31.1%), alternation of consciousness (21.1%) and papilledema (15.4%). The most frequency of risk factors of CVST were OCP consumption in women (38.5%).

Table 2 Initial clinical presentation and predisposing factors of all 39 CVST patients

	No.	%
Manifestation		
Headache	29	74.4%
Motor weakness	16	41%
Seizure	12	31.6%
Altered consciousness	8	21.1%
Papilledema	6	15.4%
Sensory disturbance	2	5.1%
Aphasia	2	5.1%
Cranial nerve involvement (Isolated CN6 palsy)	1	2.6%
Neglect	1	2.6%
Visual field defect	1	2.6%
Hypersomnolence	1	2.6%
Predisposing factor of CVST		
Oral contraception	15	38.5%
Head and neck infection	2	5.1%
SLE	1	2.6%

At the beginning, all the patients were categorized into four groups based on predominant signal intensity on T1 and T2 weight sequence MR imaging. The number of each stage is shown in Figure 1.

Figure 1 Number of each stage of thrombus



For primary outcome analysis, we selected only the interested groups to analysis: acute stage (Group 1) and early subacute stage (Group 2). Characteristic of patients at baseline in each group were shown in Table 3. The median age in acute group was 38 years (range 34-52) versus early subacute group, the median age was 39.5 years (range 25.75-55.5). Female was predominant in both group 92.3% vs 62.5%. At presentation, median GCS was 15 in both groups. The modified Rankin scale (mRS) at presentation was categorized into good (mRS2) and poor (mRS >2). In acute group, patients were measured 38.5% in good functioning and 61.5% in poor functioning, compared with early subacute group 75% were good and 25% were poor. Hemorrhage at onset were detected in both groups, 4 (30.8%) patients in acute and 3 (37.5%) patients in early subacute group. For location of sinus occluded, MRI showed the most frequent sinus involvement in both groups were superior sagittal sinus (84.6% vs 62.5%), followed by multiple sinus involvement (53.8% vs 50%)

Outcomes

While hospitalization, after initiation of anticoagulant progression of disease and major complication were noted. Most of the patients in both groups had neurological improvement or stable (61.5% vs 87.5%). Although, some of the patients had neurological deterioration (38.5% vs 12.5%). The major complication in acute group were progressive hemorrhage (60%), systemic bleeding (20%) and infection (pneumonia 20%). In early subacute, one of the patients had progressive hemorrhage.

Among the acute group, two patients died in hospital, 7 (53.8%) had good outcomes and 6 (46.3%) had poor outcomes at discharge. During 3 to 6 months of outpatient follow-up, 9 (69.2%) had good outcomes and 4 (30.8%) had poor outcomes. Compared to the early subacute group, all of them had good functioning outcomes at discharge and follow-up.

No significant correlated between age of thrombus with progression of disease (P=0.336) and complication (P=1.000) as shown in Table 4. Although, there was significant correlation between functional outcome at discharge and age of thrombus (P=0.046) (Table 5), by acute stage of thrombus had a good outcome 53.8% and poor outcome for 46.2%, while all of early subacute stage of thrombus had a good outcome.

Table 3 Characteristic of patients at baseline in acute and early subacute stage of thrombus

Characteristic	No. (%)		*p-value*
	Acute stage N=13 (%)	Early subacute stage N=8 (%)	
Median age (IQR), year	38 (34-52)	39.5 (25.75-55.5)	0.913
Gender			0.253
Male	1 (7.7)	3 (37.5)	
Female	12 (92.3)	5 (62.5)	
Median Glasglow coma scale (IQR)	15 (10.5-15)	15	0.142
mRS at presentation			0.183
mRS 0-2	5 (38.5)	6 (75)	
mRS 3-5	8 (61.5)	2 (25.0)	
Hemorrhage at onset			1.000
Yes	4 (30.8)	3 (37.5)	
No	9 (69.2)	5 (62.5)	
Location of thrombus			
Cortical vein	5 (38.5)	2 (25.0)	0.656
Superior sagittal sinus	11 (84.6)	5 (62.5)	0.325
Transverse sinus	5 (38.5)	2 (25.0)	0.656
Sigmoid sinus	4 (30.8)	2 (25.0)	1.000
Straight sinus	0	0	-
Deep venous system	2 (15.4)	2 (25.0)	0.618
Multiple sinus involvement	7 (53.8)	4 (50.0)	1.000

Table 4 progression and complication in acute and subacute stage of thrombus

	No. (%)		
	Acute stage N=13 (%)	Early subacute stage N=8 (%)	p-value
Progression			0.336
Neurological improvement or stable	8 (61.5)	7 (87.5)	
Neurological deterioration or coma	5 (38.5)	1 (12.5)	
Complication			1.000
Progressive hemorrhage	3 (60.0)	1 (100)	
Systemic bleeding	1 (20.0)	0	
Infection	1 (20.0)	0	

Table 5 Relationship between age of thrombus and primary outcomes.

Outcomes	No. (%)		
	Acute stage N=13 (%)	Early subacute stage N=8 (%)	*p-value*
At discharge			0.046
Good outcome mRS 0-2	7 (53.8)	8 (100)	
Poor outcome mRS 3-6	6 (46.2)	0	
At follow-up 3 to 6 months			0.131
Good outcome mRS 0-2	9 (69.2)		
Poor outcome mRS 3-6	4 (30.8)		

Discussion

In our study, the mean age of overall patients affected young people, and women were more often affected than men. The most frequently identified risk factors in our study were OCP. This observation is consistent with the majority of studies, such as Pakistan, India, and other developed countries.[1,2,5,13-15] Clinical presentations of this cohort are generally in consistent with what has been previously reported in other studies.[5]

According to a recent study, characteristics like advanced age, coma upon onset, hemorrhagic infarction, and clot burden score were linked to a poor outcome. All those variables that may influence a patient's outcomes were documented in our record, and baseline characteristics in both the acute and early subacute groups were not different.

This study also focused on the outcome of acute stage and early subacute stage of thrombus. We hypothesized that the age of the thrombus would correlate with the functioning outcomes of the patient and that the early subacute stage of the thrombus would be resistant to anticoagulant due to high fibrin density. Chandrashekar et al reported in previous study about high fibrin density within 1-14 days after clot presentation, which may be more resistant to fibrinolysis result in poor outcome in these stages.[2] However, overall outcome in our study was good in both groups: 71.4% of patients had independent survival (mRS<2) and 28.6% had moderate to severe dependency (mRS 3-5). Possible explanations for this discrepancy include a small sample size in each group and the influence of the details of the clot burden score. In a retrospective study, Shaban et al. looked at 115 patients who were admitted to University of Iowa Health Care with CVST between 2004 and 2014 and calculated clot burden scores as the total of thrombosis degrees in various vessels, including both cerebral veins (cortical veins, internal cerebral, Rosenthal vein, vein of Galen) and cerebral sinuses (superior sagittal, inferior sagittal, straight, torcula, transverse/sigmoid), which revealed that clot burden in cerebral veins was associated with worse discharge.[9] However, in contrast to those studies, we were unable to capture additional details about the location of cerebral veins in our investigation, which may be a restriction at this time. On the other hand, due to a lower proportion of hemorrhagic

infarction in our early subacute group (14.2%), it has been proposed that hemorrhagic infarction is associated with a poor prognosis.[6-8] There are also some limitations to our study. First of all, selection bias was unavoidable. Secondly, some of the screening tests, such as the evaluation of protein S and protein C levels, were only performed at admission, and no dynamic follow-up data was obtained.

Conclusion

Our study reveals that age of thrombus from T1-weight and T2-weight sequence MR imaging (MRI) were correlation with functioning outcome at discharge. These findings should be further verified by future well-designed clinical trials in Thailand.

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